J Gynecol Oncol. 2024 Mar;35(2):e14
https://doi.org/10.3802/jgo.2024.35.e14
pISSN 2005-0380·eISSN 2005-0399

JOURNAL OF GYNECOLOGIC ONCOLOGY

Original Article

Feasibility of laparoscopic Visceral-Peritoneal Debulking (L-VPD) in patients with stage III–IV ovarian cancer: the ULTRA-LAP trial pilot study

Roberto Tozzi, Marco Noventa, Carlo Saccardi, Giulia Spagnol, Orazio De Tommasi, Davide Coldebella, Matteo Marchetti

Division of Women's and Children Health, Department of Gynecology and Obstetrics, Padova University Hospital, Padova, Italy

Received: Apr 1, 2023
Revised: Sep 10, 2023
Accepted: Oct 3, 2023
Published online: Oct 16, 2023

Correspondence to
Roberto Tozzi
Division of Women's and Children Health, Department of Gynecology and Obstetrics, Padova University Hospital, Via Nicolò Giustiniani 3, Padova 35121, Italy.
Email: roberto.tozzi@unipd.it

ORCID iDs
Roberto Tozzi
https://orcid.org/0000-0001-6123-1628
Marco Noventa
https://orcid.org/0000-0002-7809-6001
Carlo Saccardi
https://orcid.org/0000-0001-7476-997X
Giulia Spagnol
https://orcid.org/0000-0003-3525-0571
Orazio De Tommasi
https://orcid.org/0000-0001-5890-9792
Davide Coldebella
https://orcid.org/0000-0002-8923-9135

ABSTRACT

Objective: A non-randomized prospective clinical trial (ULTRA-LAP) was registered to test safety, side effects and efficacy of laparoscopic Visceral-Peritoneal Debulking (L-VPD) in patients with stage III–IV ovarian cancer (OC). A pilot study was designed to identify which OC patients are suitable to undergo L-VPD.
Methods: Between March 2016 and October 2021, all consecutive patients with OC underwent exploratory laparoscopy (EXL). All patients whose disease was deemed amenable for a complete resection (CR) at imaging review and EXL, underwent VPD. In all patients a consistent attempt was made at completing L-VPD.
Results: Two hundred and eight OC had EXL in the study period: 121 underwent interval VPD and 87 up-front VPD. Overall, 158 patients had VPD by laparotomy (75.9%) and 50 (24.1%) had L-VPD, of which 34 patients as interval (iL-VPD) and 16 as up-front (uL-VPD). Intra- and post-operative morbidity was very low in the L-VPD group. CR rate was 98% in L-VPD group and 94% in VPD. Most common reason for conversion was diaphragmatic disease extending dorsally.
Conclusion: In the pilot study of ULTRA-LAP, L-VPD was completed in 24,1% of OC. Initial analysis supports the feasibility of L-VPD in 2 groups of OC: those with no gross disease at interval surgery and those with gross visible disease at upfront or interval surgery, but limited to: pelvis (including recto-sigmoid), gastro colic omentum, peritoneum and diaphragm, the latter not requiring dorsal liver mobilization. Both groups had 100% feasibility and have been thus forth recruited to ULTRA-LAP.

Trial Registration: ClinicalTrials.gov Identifier: NCT05862740

Keywords: Ovarian Cancer; Visceral-Peritoneal Debulking; Laparoscopic Debulking; Minimally Invasive Debulking Surgery

JOURNAL OF GYNECOLOGIC ONCOLOGY

Matteo Marchetti
https://orcid.org/0000-0003-4427-0101

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Trial Registration
ClinicalTrials.gov Identifier: NCT05862740

Author Contributions
Conceptualization: T.R.; Data curation: T.R., N.M., S.G., D.O., C.D., M.M.; Formal analysis: T.R., N.M., S.G., D.O., C.D., M.M.; Investigation: T.R., S.C., M.M.; Methodology: T.R.; Project administration: T.R.; Supervision: T.R.; Validation: N.M., S.C., M.M.; Writing - original draft: T.R.; Writing - review & editing: T.R., M.M.

Synopsis
The pilot study succeeded to identify the most suitable patients to recruit in the ULTRA-LAP trial. Patients with complete response to chemotherapy and patients at primary or interval surgery with disease limited to the pelvis (including sigmoid-rectum resection), any peritoneum, omentum and diaphragmatic peritoneum (not requiring hepato-caval mobilization) had 100% feasibility rate at laparoscopic Visceral-Peritoneal Debulking (L-VPD). Feasibility of L-VPD was 24.1%, efficacy was measured as 98% CR. Safety was established by the absence of port site metastasis and patients with early recurrence at 22 months median follow-up.

INTRODUCTION

Ovarian cancer (OC) is an aggressive disease. Over 75% of women at initial diagnosis with intra-peritoneal spread and/or involvement of extra-abdominal organs are classified as International Federation of Gynecology and Obstetrics stage III–IV [1,2]. The standard of treatment is a combination of surgery and chemotherapy [3,4]. Lately, significant progress in survival has been achieved owing to the introduction of new drugs [5]. A complete resection (CR) of all visible disease is unanimously associated with the best survival rate [6-10]. In the last 20 years, the surgical research in gynecologic oncology has vastly expanded the portfolio of procedures to achieve the highest rate of CR. It is now common to perform upper abdominal surgery [11-13], single/multiple bowel resections [14,15], diaphragmatic and cardio-thoracic surgery [16-20]. The contribution of surgery to OC is witnessed by the undisputed prognostic significance of the CR, irrespective of the initial treatment modality. It is therefore justified that gynecologic oncologists strive to increase CR rate to the highest possible. Alongside this, the effort has been to reduce the surgical morbidity. In this scenario, the ultimate attempt has been, in recent years, the use of laparoscopy to complete the whole surgical debulking [21,22]. Two trials have been published on the laparoscopic treatment of OC: the MISSION and CILOVE trials [23,24]. Both trials focused on patients who underwent neoadjuvant chemotherapy. The MISSION trial included patients with a complete response to chemotherapy and the CILOVE trial had very restrictive inclusion criteria for surgery. In 2016, we registered a service evaluation at the Oxford University Hospital, on the feasibility of Visceral-Peritoneal Debulking (VPD) by laparoscopy (L-VPD) in OC after chemotherapy. Later on, encouraged by the early data, we extended inclusion criteria of the clinical trial to all patients with OC, registering the ULTRA-LAP trial. Here, we report the results of the pilot study designed to identify the most suitable candidates to include in the phase II of the ULTRA-LAP trial.

MATERIALS AND METHODS

1. Study design and patient eligibility

ULTRA-LAP is an ongoing, phase I-II, multicenter, open label, clinical trial designed to investigate the safety, morbidity and efficacy of laparoscopic surgery in OC. In 2016, we registered a service evaluation project in Oxford and obtained Oxford University Hospital Trust approval (number 3267). The study was initially offered to all consecutive OC patients, who underwent neo-adjuvant chemotherapy and presented any response or stable disease after chemo. Later on, we expanded the study to include patients who were candidates to up-front surgery and the study was approved as a prospective phase I-II clinical trial at the University

https://doi.org/10.3802/jgo.2024.35.e14

of Padua Hospital (ID 5497/AO/22). It was registered on ClinicalTrials.gov in May 2023 (ID: NCT05862740). We conducted a pilot study, a miniature anticipation of the ULTRA-LAP trial, focused on study feasibility, safety, and identification of suitable patients to enroll in ULTRA-LAP. All consecutive patients with histologically documented OC and referred to our institution, were offered ULTRA-LAP. Inclusion and exclusion criteria recall those we previously published for VPD [25] and are reported in **Table 1**. Patients with disease precluding CR, based on pre- or intra-operative exclusion criteria (**Table 1**), were not offered VPD and addressed to neoadjuvant chemotherapy. In the latter group, response to neoadjuvant chemotherapy was assessed based on Gynecological Cancer InterGroup (GCIG) and Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1 criteria [26]. At computed tomography (CT) scan review, we classified response as: complete (no visible disease), good partial (>50% reduction), partial (<50% reduction), or stable disease. Disease progression on chemotherapy was an exclusion criterion. Details of the VPD protocol were previously reported [25]. All OC underwent pre-operative imaging review at the gynecologic oncology multi-disciplinary team (MDT) meeting. Once patients were discussed at the MDT meeting with imaging review, an exploratory laparoscopy (EXL) would always follow to confirm eligibility for VPD. The single accepted goal for VPD was CR of all visible disease. All consecutive OC in the study period underwent a consistent attempt to accomplish the whole surgery by laparoscopy. If a CR was not achievable by laparoscopy but the surgeon felt it could be by laparotomy, the operation was converted at once. Timing and reason for conversion to laparotomy were accurately recorded for each patient. Conversion rate, short- and long-term morbidity was also documented. Likewise, we recorded stage, histology, response to chemotherapy (in patients deemed to be not feasible for upfront surgery), disease load at time of surgery (using the Fagotti score), surgical procedures performed and residual disease, if any. For patients included in both VPD group (performed by laparotomy) and L-VPD group, data analysis was broken down in up-front and Interval surgery. Following VPD or L-VPD, a CT scan preceded the beginning of chemotherapy to confirm the surgical result with regards to residual disease. In case of questionable radiologic findings, the patient was discussed at the MDT meeting again and followed up with serial CT scans or referred for further surgery. All patients signed the study enrollment documents and a specific consent which was approved by the institutional ethic committee.

2. Surgical technique of L-VPD

The operation started as an EXL to rule out exclusion criteria (**Table 1**) for a CR. Only atraumatic instruments, bipolar scissors and graspers (Karl Storz, Tuttlingen, Germany) were used for the diagnostic part including adhesiolysis and dissection. Once exclusion criteria were excluded through direct vision, the extension of the disease was examined thoroughly by pursuing dissection and mobilization, to finally elect patients to L-VPD. We used 2×10 mm (in the umbilicus and the Palmer's point) and 3×5 mm trocars (in the lower abdomen) which were placed in the usual positions (**Fig. S1**). Since the pelvis was never a cause of conversion to laparotomy, we always started from the upper abdomen. In patients where

Table 1. Criteria for visceral-peritoneal debulking [25]

Inclusion criteria	Exclusion criteria
Pre-operative:	Pre-operative:
- Histology proven or suspected stage IIIC–IV ovarian cancer	- Lung metastases
- Performance status ≤ECOG 2	- Three or more liver segments involvement
- Any response or stable disease to chemotherapy in neo-adjuvant pathway	- Disease progression on chemotherapy
	Intra-operative:
	- Diffuse small bowel serosal deposits
	- Porta hepatis encasement

ECOG, Eastern Cooperative Oncology Group Performance Status Scale.

https://doi.org/10.3802/jgo.2024.35.e14

the diaphragmatic disease was evident, a proper liver mobilization was completed until the extent of disease could be fully assessed [17]. Same approach was used to assess gastro-splenic and gastro-colic omental disease. The lesser sac was entered through the gastro-epiploic arcade to separate, if possible, the meso-colon and the omentum, and to identify the stomach and the pancreas. Additional ports were placed, if necessary, below the subcostal margin either in the pararectal line, the anterior axillary line or the posterior axillary line. The gastro-colic disease was assessed, particularly if adherent to the transverse colon. The concomitance of a transverse colon resection and a sigmoid-rectum resection was considered challenging at laparoscopy. The pelvis was assessed for the need of a sigmoid rectum resection. Once concluded that CR was achievable, the actual resection started. Surgical techniques for diaphragmatic surgery [13] and en-bloc resection of the pelvis including sigmoid rectum resection [14] have already been reported.

3. Endpoints and statistical analysis

The principal aim of this pilot study was to identify the most suitable sub-group of patients to include in ULTRA-LAP. We recorded tumor stage, initial treatment and anatomic site of disease, to identify an OC group that had the highest chance of the whole VPD completed by laparoscopy. Concomitantly, the feasibility was tested (defined as the rate of surgery completed by laparoscopy). Because this part of the study was preparatory to ULTRA-LAP, safety (rate of complications specifically caused by the technique and rate of patients with an early recurrence compared to the laparotomy group) and efficacy (rate of surgery ended with CR) were also measured. Morbidity was reported using the Clavien-Dindo classification. Although not considered strictly necessary, a sample size calculation was made for the feasibility part of ULTRA-LAP based on the Julious method [27]. The aim of the calculation was to determine the smallest number of patients to significantly test safety, so as to avoid futility or unnecessary danger to patients. If 4 patients had displayed early recurrence following a CR (defined as <4 months from completion of treatment), a first warrant was issued. Had 2 further patients displayed early recurrence, the study was interrupted. At the same time the sample size needed to be large enough to support feasibility. The calculation identified 24 patients as the number that would test safety (surgical and oncologic) and feasibility with a sufficient confidence interval. For the ULTRA-LAP trial, the Simon method [28] was used. In OC patients with gross disease, we anticipated a conversion rate of 80%, morbidity <20% and superimposable survival to the traditional surgery group. We calculated 62 patients to be a sufficient number to achieve a 90% power with a 5% significance. We also used a very tight futility test on early recurrence. An initial warning was issued if 2 patients displayed tumor recurrence within the first 12 months of the operation. A final warning was going to follow, if 2 additional patients experienced recurrence within 12 months. The trial was discontinued if more than 10% of the study group displayed recurrence within the first 12 months. Once the data were collected, we used the chi-square test or Fisher's exact test to compare categorical variables, and the Student's t-test for continuous variables. A p value of ≤0.05 was considered statistically significant. The comparison was necessary within the L-VPD group to identify patients eligible to ULTRA-LAP, but had limited significance between VPD and L-VPD groups since the former had more complex surgery.

RESULTS

A flowchart of the study is in **Fig. 1**. Patient demographics and tumor characteristics are reported in **Table 2**. Two hundred and eight OC patients were suitable for VPD in the study

https://doi.org/10.3802/jgo.2024.35.e14

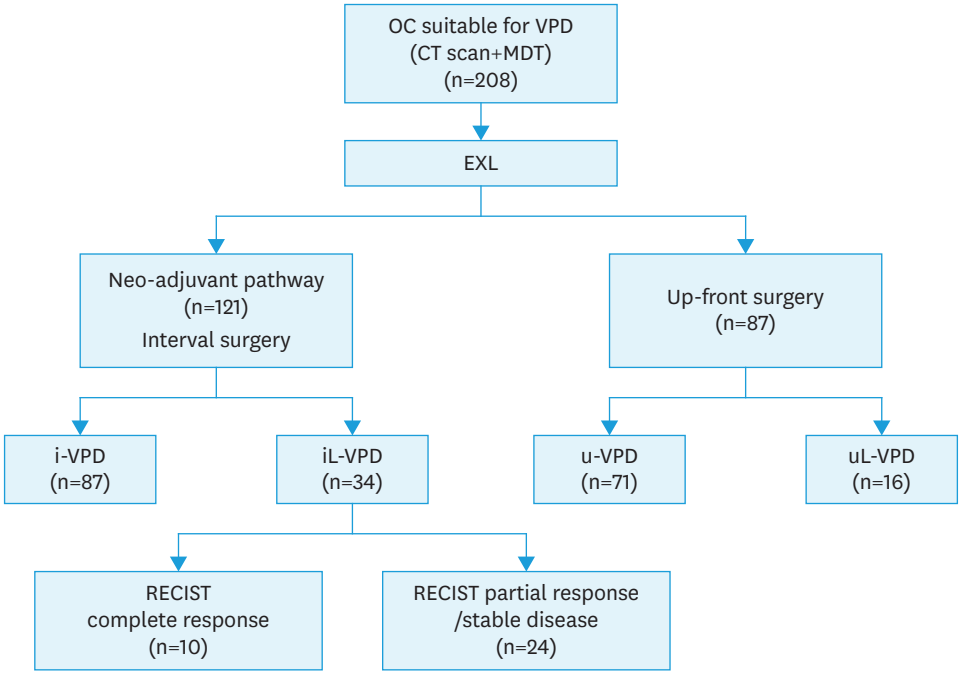

Fig. 1. Patient's flow-chart of the ULTRA-LAP trial pilot study.
CT, computed tomography; EXL, exploratory laparoscopy; iL-VPD, interval laparoscopic visceral-peritoneal debulking; i-VPD, interval visceral-peritoneal debulking; MDT, multidisciplinary team; uL-VPD, up-front laparoscopic visceral-peritoneal debulking; u-VPD, up-front visceral-peritoneal debulking; VPD, visceral-peritoneal debulking.

period (2016 March to 2021 October) and underwent EXL: 164 were stage IIIC and 44 were stage IV. One hundred and twenty one patients entered the neo-adjuvant pathway and 87 underwent up-front surgery. After 3 cycles of treatment, response to chemotherapy was complete in 10 patients, good partial in 38, partial in 51 and stable disease was found in 22 patients. At time of surgery, disease load was a Fagotti score of 8 or higher in all up-front VPD (u-VPD) patients and in 84 patients out of 121 (69.4%) in the interval VPD (i-VPD) group.

Table 2. Patient demographics and tumor characteristics (n=208)

Characteristics	VPD	L-VPD	p-value
Patients, n/tot, (%)	158 (76.0)	50 (24.0)	<0.05
Age (yr)	68 (54–78)	62 (51–74)	0.7
Histology			0.7
HGSOC	130 (82.3)	40 (80.0)	
Non HGSOC	28 (17.7)	10 (20.0)	
FIGO stage			0.6
IIIC	120 (75.9)	44 (88.0)	
IV	38 (24.1)	6 (12.0)	
u-VPD	71 (44.9)	16 (32.0)	0.1
i-VPD	87 (55.1)	34 (68.0)	
CA-125 U/mL at diagnosis	819 (129–3,670)	645 (112–1,187)	<0.05
CA-125 U/mL at i-VPD	190 (15–615)	90 (5–250)	<0.005
ECOG 0–1	48 (30.4)	31 (62.0)	<0.005
ECOG 2	110 (69.6)	19 (38.0)	

Values are presented as number (%) or mean (range).
CA-125, cancer antigen 125; ECOG, Eastern Cooperative Oncology Group Performance Status Scale; FIGO, International Federation of Gynecology and Obstetrics; HGSOC, high grade serous ovarian cancer; i-VPD, interval visceral-peritoneal debulking; L-VPD, laparoscopic visceral-peritoneal debulking; u-VPD, upfront visceral-peritoneal debulking; VPD, visceral-peritoneal debulking.

https://doi.org/10.3802/jgo.2024.35.e14

JOURNAL OF GYNECOLOGIC ONCOLOGY

Table 3. Reasons for conversion to laparotomy (n=158)

Reasons	Value
Diaphragmatic disease extended dorsally	66 (41.8)
Matted spleno-pancreatic disease	27 (17.1)
Gastro-splenic omental disease	22 (13.9)
Multiple bowel segments involvement	19 (12.0)
Omental disease invading/inseparable from the transverse colon	16 (10.1)
Others	8 (5.1)

Values are presented as number (%).

Overall, 158 patients (76.0%) had the surgery converted to laparotomy to complete VPD: 87 had i-VPD and 71 u-VPD. Fifty patients (24.0%) had L-VPD: 34 as iL-VPD and 16 as uL-VPD. In patients whose surgery was converted to laparotomy, EXL lasted on average 48 minutes (range, 7–113). Reasons for conversion to laparotomy in 158 patients are reported in **Table 3** and the most frequent was diaphragmatic disease extending dorsally (41.8%). In the i-VPD group, 10 patients out of overall 121 (8.2%) were found with no gross visible disease at time of surgery. In these 10 patients, laparoscopic surgery was consistent with hysterectomy, bilateral salpingo-oophorectomy, omentectomy and peritoneal biopsies. No conversion occurred and all patients went home within 48 hours. Five out of 10 had microscopic residual disease in the final histology. In **Table 4** all surgical procedures performed divided by groups are reported. Excluding 10 patients with no gross visible disease at i-VPD after chemotherapy, the rate of sigmoid-rectum resection, diaphragmatic surgery, omentectomy and peritonectomy was not significantly different between VPD and L-VPD groups. Rate of pleurectomy, splenectomy, tail pancreas resection, hepato-celiac lymphadenectomy was significantly higher in the VPD group. Average surgical time was not significantly different (326' vs. 341', p=0.03), mean post-op hospitalization time was significantly shorter in the L-VPD group (4 vs. 11 days, p=0.02). Overall complications rate was significantly higher in the VPD group (21% vs. 8%, p=0.03). Grade 3 and 4 complications were also significantly higher in the VPD group (6.9% vs. 1.8%, p=0.017). Four patients experienced complications in the L-VPD group: 3 were graded as 1–2 (1 × prolonged ileus, respiratory, urinary infection) and 1 graded as 3 (second laparoscopy

Table 4. Surgical procedures and outcomes (n=208)

Variables	VPD (n=158)	L-VPD (n=50)	p-value
Average surgical time (min)	341	326	0.3
Mean hospitalization (days)	11	4	<0.05
Complete resection (R=0)	149 (94.3)	50 (100.0)	0.8
Procedures			
S-R resection	102 (64.5)	32 (64.0)	0.9
Diaphragmatic surgery	126 (79.7)	36 (72.0)	0.7
Omentectomy	158 (100.0)	50 (100.0)	0.9
Peritonectomy	140 (88.6)	36 (72.0)	0.4
Pleurectomy	32 (20.2)	-	-
Splenectomy	29 (18.3)	2 (4.0)	<0.05
Tail-P resection	12 (7.6)	-	-
H-C lymphadenectomy	18 (11.3)	-	-
Complete response to chemotherapy	-	10/34 (29.4)	
Begin/Restart chemotherapy (days)	42 (38–59)	27 (18–41)	<0.05
Complications			
Overall	33 (20.8)	4 (8.0)	<0.05
G3-G4	11 (6.9)	1 (1.8)	<0.05

Values are presented as number (%) or mean (range).
CHT, chemotherapy; H-C, hepato-celiac; i-VPD, interval visceral-peritoneal debulking; L-VPD, laparoscopic visceral-peritoneal debulking; S-R, sigmoid-rectum; Tail-P, tail of the pancreas; VPD, visceral-peritoneal debulking.

https://doi.org/10.3802/jgo.2024.35.e14

after incomplete resection as described below). Complete resection of all visible disease was accomplished in 98% of the L-VPD patients and in 94% of the VPD group. CT scans were performed in all patients before the start of chemotherapy. In 1 patient, a 2.4 cm nodule was found in the Morison pouch missed at time of L-VPD. The patient was re-discussed at the MDT and underwent a second procedure at which the nodule was identified and removed by laparoscopy. Patients in the L-VPD group started or re-started chemotherapy averagely 15 days before the VPD group (27 vs. 42 days). No patients in the L-VPD group experienced recurrence within the first 12 months after surgery. The breakdown of the L-VPD group patients allowed to stratify for the probability of a successful completion of the procedure. In patients with no gross visible disease after chemotherapy 100% success rate was achieved. Overall, patients in the i-VPD group had a significantly higher chance than the u-VPD to have the procedure completed by laparoscopy (28% vs. 18.3%, p=0.02). Excluding patients with a complete clinical response to chemotherapy, 24 out of 111 (21.6%) patients with gross visible disease had their surgery completed by laparoscopy. Likewise, patients with stage IIIC also had significantly higher chances then patients with stage IV. Finally based on the disease load and dissemination, we identified a group of patients who had the highest chance of a complete L-VPD. They had disease confined to the pelvis (not excluding sigmoid-rectum and peritoneal invasion), gastro-colic omentum not invading the meso-colon, peritoneum and diaphragmatic disease, the latter not requiring a dorsal liver mobilization. In these group of patients, irrespective of initial treatment, we recorded a 100% feasibility. The results of this pilot study have been incorporated in the ULTRA-LAP trial to select the most suitable candidates to be recruited in the trial.

DISCUSSION

The treatment of OC is a combination of surgery and chemotherapy. None of the two is sufficient and both are preparatory for the other. While the advent of new drugs has significantly improved disease-free interval with maintenance therapy [29,30], surgery is increasing the rate of patients left with no residual disease by accomplishing more complex resection of disease. The ideal goal is to do the latter by reducing the morbidity of the procedures. As it occurred in other branches of surgical oncology and in gynecologic oncology, the advent of laparoscopy was associated with extraordinary advantages for the patients. Shorter hospitalization, decreased rate of infection, thrombo-embolic events and need for analgesia were some of the features that made laparoscopy being the standard of care for most patients with malignancies. In patients with ovarian cancer, the use of laparoscopy was limited to women with early disease. Lately the use of laparoscopy was extended to patients with advanced disease to help identify women with disease amenable to complete resection [31,32]. As previously mentioned, 2 recent studies, the CILOVE and MISSION trials [23,24], were published. From the latter a subsequent international multi-centric trial stemmed [33]. Both trials recruited OC patients in the neo-adjuvant chemotherapy pathway. The MISSION trial included patients with a complete clinical response to chemotherapy and the CILOVE adopted very restrictive criteria on the type of disease present. Indeed, peritoneal supra-mesocolic disease, pelvic mass >10 cm and supra-centimetric lymphadenopathy were exclusion criteria. Summing the patients in all 3 publications, the trials included around 150 patients. As a result of the selection process, the surgical procedures included in these trials very rarely exceeded the hysterectomy, bilateral salpingo-ophorectomy and omentectomy. Overall, bowel resection occurred in 3 patients and diaphragmatic peritonectomy in 6 patients out of 150. Traditionally, the rate of complete

https://doi.org/10.3802/jgo.2024.35.e14

clinical response to chemotherapy in OC is around 5% [34]. Likewise, the chance that OC do not have any upper abdominal disease at interval surgery is scarce. It is fair to say that the study population included in these trials only represent a niche of OC patients. In centers with high patient volume, most women will undergo up-front surgery. Those who enter the neo-adjuvant chemotherapy will most likely need upper abdominal surgery and procedures beyond the ones included in these trials. Therefore, irrespective of initial treatment modality, the most common surgical treatment for OC is multi-visceral debulking. In this scenario, ULTRA-LAP is currently the only trial addressing the feasibility of multi-visceral debulking surgery in OC. Present data from the pilot study confirm the feasibility of laparoscopic interval surgery in patients recruited in the neo-adjuvant chemotherapy who had a complete response. New finding from this study is the feasibility of L-VPD in patients with gross visible disease after a partial response to neo-adjuvant chemotherapy. Also, this study supports feasibility of L-VPD in a minority of patients at up-front surgery. Overall, the ULTRA-LAP pilot study identified a group of patients whose disease was amenable for laparoscopic surgery based on the anatomic location of disease and irrespective of their initial treatment. In OC with any pelvic disease, gastro-colic omental, peritoneal and diaphragmatic disease, not requiring hepato-caval dissection, a 98% CR rate was achieved.

The data were extremely encouraging in terms of safety and efficacy. Complications rate was significantly lower than standard surgery and efficacy was unaltered reaching 98% CR rate, because one patient needed two procedures. These data reflect an initial effort on the use of laparoscopic surgery in completing multi-visceral in OC. The most relevant information is that the laparoscopic approach did not cause worse prognosis or higher morbidity. Accounting for the different study group, it offered a significantly better surgical outcome to OC patients. The prosecution of ULTRA-LAP will provide larger data on the feasibility, safety and efficacy of multi-visceral debulking in OC which were selected through the pilot study. Another interesting aspect of laparoscopy is the potential impact on inflammation and immune system. Considering the heterogeneity of ovarian cancer, there is a great attention to the role played by inflammation and immune system in tumor progression and resistance [35]. Laparotomy is traditionally associated with a significant level of post-operative inflammation and immune depression. In that respect, there are sufficient data to show that laparoscopy is associated with a lower level of immunodepression and less inflammation [36]. The immediate outcome is the faster restoration of bowel movements for example, but also the faster return to normal levels of C-reactive protein and white cell count. If this translates into a better oncologic outcome, it needs to be proved. Surely it conveyed a faster recovery with shorter hospitalization and earlier return to domestic life, which are relevant outcomes.

ULTRALAP trial is a pioneering experience with all the limits of the ground breaking investigation. It is testing a new surgical technique within the frame of a controlled, registered, prospective study. The pilot study has the novelty of data which were never reported before and is based on the work of a team with a recognized experience in laparoscopy and gynecologic oncology. The data were every encouraging on all endpoints. However, they were inherently dependent on the surgical expertise and on the inevitable selection. It is therefore impossible, at this point, to standardize criteria for L-VPD or derive prognostic factors for a successful completion. Indeed, one of the potential pitfalls of the ULTRA-LAP trial is to expand it and include other centers. While they were considerably ample, our criteria can be enlarged by other surgeons and by our team. Another clear limitation of the pilot study is that the VPD group was comprised of patients in which the L-VPD failed. VPD group had more extensive disease, more complex surgery and more

https://doi.org/10.3802/jgo.2024.35.e14

challenging patients. Accordingly, the comparison between the 2 groups can only serve the purpose to rule out a worse outcome in the L-VPD group.

This pilot study was extremely useful in identifying the initial population to recruit in the phase II trial. It also helped excluding a detrimental impact of laparoscopy on surgical and survival outcomes. Once overcome the futility test at 12 months in the pilot study, we can safely continue with the recruitment in the phase II trial. The latter will, no doubt, provide more information and solid data on L-VPD.

SUPPLEMENTARY MATERIAL

Fig. S1

Trocars positioning for L-VPD. Port site position for laparoscopy using 10 mm-optic and 5 mm-ancillary trocars

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359-86. PUBMED | CROSSREF
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7-30. PUBMED | CROSSREF
3. Wright AA, Bohlke K, Armstrong DK, Bookman MA, Cliby WA, Coleman RL, et al. Neoadjuvant chemotherapy for newly diagnosed, advanced ovarian cancer: Society of Gynecologic Oncology and American Society of Clinical Oncology Clinical Practice Guideline. Gynecol Oncol 2016;143:3-15. PUBMED | CROSSREF
4. Rauh-Hain JA, Melamed A, Wright A, Gockley A, Clemmer JT, Schorge JO, et al. Overall survival following neoadjuvant chemotherapy vs primary cytoreductive surgery in women with epithelial ovarian cancer: analysis of the national cancer database. JAMA Oncol 2017;3:76-82. PUBMED | CROSSREF
5. Colombo N, Sessa C, Bois AD, Ledermann J, McCluggage WG, McNeish I, et al. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease. Int J Gynecol Cancer 2019;30:672-705. PUBMED | CROSSREF
6. Curtin JP, Malik R, Venkatraman ES, Barakat RR, Hoskins WJ. Stage IV ovarian cancer: impact of surgical debulking. Gynecol Oncol 1997;64:9-12. PUBMED | CROSSREF
7. Redman JR, Petroni GR, Saigo PE, Geller NL, Hakes TB. Prognostic factors in advanced ovarian carcinoma. J Clin Oncol 1986;4:515-23. PUBMED | CROSSREF
8. Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. J Clin Oncol 2002;20:1248-59. PUBMED | CROSSREF
9. Shih KK, Chi DS. Maximal cytoreductive effort in epithelial ovarian cancer surgery. J Gynecol Oncol 2010;21:75-80. PUBMED | CROSSREF
10. Eisenkop SM, Spirtos NM. Procedures required to accomplish complete cytoreduction of ovarian cancer: is there a correlation with "biological aggressiveness" and survival? Gynecol Oncol 2001;82:435-41. PUBMED | CROSSREF
11. Eisenhauer EL, Chi DS. Liver mobilization and diaphragm peritonectomy/resection. Gynecol Oncol 2007;104:25-8. PUBMED | CROSSREF
12. Fanfani F, Fagotti A, Gallotta V, Ercoli A, Pacelli F, Costantini B, et al. Upper abdominal surgery in advanced and recurrent ovarian cancer: role of diaphragmatic surgery. Gynecol Oncol 2010;116:497-501. PUBMED | CROSSREF
13. Tozzi R, Ferrari F, Nieuwstad J, Campanile RG, Soleymani Majd H. Tozzi classification of diaphragmatic surgery in patients with stage IIIC-IV ovarian cancer based on surgical findings and complexity. J Gynecol Oncol 2020;31:e14. PUBMED | CROSSREF

14. Tozzi R, Gubbala K, Majd HS, Campanile RG. Interval laparoscopic en-bloc resection of the pelvis (L-EnBRP) in patients with stage IIIC-IV ovarian cancer: description of the technique and surgical outcomes. Gynecol Oncol 2016;142:477-83. PUBMED | CROSSREF
15. Tozzi R, Casarin J, Baysal A, Valenti G, Kilic Y, Majd HS, et al. Bowel resection rate but not bowel related morbidity is decreased after interval debulking surgery compared to primary surgery in patents with stage IIIC-IV ovarian cancer. J Gynecol Oncol 2019;30:e25. PUBMED | CROSSREF
16. Aletti GD, Dowdy SC, Podratz KC, Cliby WA. Surgical treatment of diaphragm disease correlates with improved survival in optimally debulked advanced stage ovarian cancer. Gynecol Oncol 2006;100:283-7. PUBMED | CROSSREF
17. Soleymani Majd H, Ferrari F, Manek S, Gubbala K, Campanile RG, Hardern K, et al. Diaphragmatic peritonectomy vs. full thickness resection with pleurectomy during visceral-peritoneal debulking (VPD) in 100 consecutive patients with stage IIIC-IV ovarian cancer: a surgical-histological analysis. Gynecol Oncol 2016;140:430-5. PUBMED | CROSSREF
18. Kapnick SJ, Griffiths CT, Finkler NJ. Occult pleural involvement in stage III ovarian carcinoma: role of diaphragm resection. Gynecol Oncol 1990;39:135-8. PUBMED | CROSSREF
19. Dowdy SC, Loewen RT, Aletti G, Feitoza SS, Cliby W. Assessment of outcomes and morbidity following diaphragmatic peritonectomy for women with ovarian carcinoma. Gynecol Oncol 2008;109:303-7. PUBMED | CROSSREF
20. Pinelli C, Morotti M, Casarin J, Tozzi R, Alazzam M, Mavroeidis VK, et al. The feasibility of cardiophrenic lymphnode assessment and removal in patients requiring diaphragmatic resection during interval debulking surgery for ovarian cancer. J Invest Surg 2021;34:756-62. PUBMED | CROSSREF
21. Melamed A, Nitecki R, Boruta DM 2nd, Del Carmen MG, Clark RM, Growdon WB, et al. Laparoscopy compared with laparotomy for debulking ovarian cancer after neoadjuvant chemotherapy. Obstet Gynecol 2017;129:861-9. PUBMED | CROSSREF
22. Lecointre L, Pellerin M, Venkatasamy A, Fabacher T, Eberst L, Gantzer J, et al. Complete laparoscopic interval debulking surgery for advanced ovarian cancer achieves similar survival outcomes to open approach: a propensity-matched study. J Invest Surg 2022;35:1394-401. PUBMED | CROSSREF
23. Pomel C, Akladios C, Lambaudie E, Rouzier R, Ferron G, Lecuru F, et al. Laparoscopic management of advanced epithelial ovarian cancer after neoadjuvant chemotherapy: a phase II prospective multicenter non-randomized trial (the CILOVE study). Int J Gynecol Cancer 2021;31:1572-8. PUBMED | CROSSREF
24. Gueli Alletti S, Bottoni C, Fanfani F, Gallotta V, Chiantera V, Costantini B, et al. Minimally invasive interval debulking surgery in ovarian neoplasm (MISSION trial-NCT02324595): a feasibility study. Am J Obstet Gynecol 2016;214:503.e1-6. PUBMED | CROSSREF
25. Tozzi R, Giannice R, Cianci S, Tardino S, Campanile RG, Gubbala K, et al. Neo-adjuvant chemotherapy does not increase the rate of complete resection and does not significantly reduce the morbidity of visceral-peritoneal debulking (VPD) in patients with stage IIIC-IV ovarian cancer. Gynecol Oncol 2015;138:252-8. PUBMED | CROSSREF
26. Schwartz LH, Litière S, de Vries E, Ford R, Gwyther S, Mandrekar S, et al. RECIST 1.1-update and clarification: from the RECIST committee. Eur J Cancer 2016;62:132-7. PUBMED | CROSSREF
27. Julious SA. Sample sizes for clinical trials with normal data. Stat Med 2004;23:1921-86. PUBMED | CROSSREF
28. Freedman LS, White SJ. On the use of Pocock and Simon's method for balancing treatment numbers over prognostic factors in the controlled clinical trial. Biometrics 1976;32:691-4. PUBMED | CROSSREF
29. Banerjee S, Moore KN, Colombo N, Scambia G, Kim BG, Oaknin A, et al. Maintenance olaparib for patients with newly diagnosed advanced ovarian cancer and a *BRCA* mutation (SOLO1/GOG 3004): 5-year follow-up of a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2021;22:1721-31. PUBMED | CROSSREF
30. González-Martín A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med 2019;381:2391-402. PUBMED | CROSSREF
31. Tozzi R, Traill Z, Campanile RG, Kilic Y, Baysal A, Giannice R, et al. Diagnostic flow-chart to identify bowel involvement in patients with stage IIIC-IV ovarian cancer: can laparoscopy improve the accuracy of CT scan? Gynecol Oncol 2019;155:207-12. PUBMED | CROSSREF
32. Tozzi R, Traill Z, Valenti G, Ferrari F, Gubbala K, Campanile RG. A prospective study on the diagnostic pathway of patients with stage IIIC-IV ovarian cancer: Exploratory laparoscopy (EXL) + CT scan VS. CT scan. Gynecol Oncol 2021;161:188-93. PUBMED | CROSSREF
33. Fagotti A, Gueli Alletti S, Corrado G, Cola E, Vizza E, Vieira M, et al. The INTERNATIONAL MISSION study: minimally invasive surgery in ovarian neoplasms after neoadjuvant chemotherapy. Int J Gynecol Cancer 2019;29:5-9. PUBMED | CROSSREF

34. LaFargue CJ, Handley KF, Fleming ND, Nick AM, Chelariu-Raicu A, Fellman B, et al. Clinical analysis of pathologic complete responders in advanced-stage ovarian cancer. Gynecol Oncol 2022;165:82-9. PUBMED | CROSSREF

35. Zhao H, Wu L, Yan G, Chen Y, Zhou M, Wu Y, et al. Inflammation and tumor progression: signaling pathways and targeted intervention. Signal Transduct Target Ther 2021;6:263. PUBMED | CROSSREF

36. Gupta A, Watson DI. Effect of laparoscopy on immune function. Br J Surg 2001;88:1296-306. PUBMED | CROSSREF